UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,484	03/25/2002	Jacques Alexandre Hatzfeld	USB 99 AH CNR SOMA	5595

466 7590 09/21/2005

YOUNG & THOMPSON
745 SOUTH 23RD STREET -
2ND FLOOR
ARLINGTON, VA 22202

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,484	HATZFELD ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 25 October 2004.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 17 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 and 18-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 December 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 6/27/05, has been entered. Claims 1-20 are pending; claims 18-20 are newly added; claim 17 is withdrawn; claims 1-16 and 18-20 are under current examination.

Election/Restrictions

Claim 17 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/25/04.

Claim Objections

The prior objection of claim 15 is withdrawn in view of Applicants' amendment to the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, and newly added claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 1/25/05.

Applicants argue that the amendments to the claims now refer to "stem cells" which are now specified as "human stem cells", and that newly added claims 19 and 20 recite "primate stem cells". Thus, Applicants argue that it is believed that the claimed invention complies with the written description requirement, furthermore, the use of TGF-β as the preferred inhibitor for cell development. Applicants argue that with regard to "human stem cells" they are exemplified as human hematopoietic stem cells (HSCs). See p. 10 of the response. Thus, Applicants argue that it would be within the ability of the skilled artisan to make minor adjustments to the experimental protocol set forth in the application to other human stem cells, and other inhibitors of cell development (or pleiotropic factors). Applicants point to various articles in order to show that the invention can be effectively implemented on various human stem cells, with various inhibitors (J. Cell Sci., 116: 4043-4052) and that the skilled artisan, upon reading the disclosure, would know which cells are within the scope of "human stem cells" and would know what the expression "inhibitor of cell development" refers to. Furthermore, the description provides guidelines for how adjustments ought to be made, so as to implement the method or process of the invention on other human stem cells. See pp. 11-12 of the Response.

These arguments have been considered, but are not found to be persuasive. The prior rejection, under written description, is not overcome by the instant amendments to the claims because they do no address the rejection. Particularly, the specification fails to provide appropriate description for the claimed embodiments of "embryonic stem cells at the origin of somatic stem cells, " stem cells at the origin of blood, and various other tissues", with any particularity to indicate that Applicants had possession of the claimed invention. In the instant case, the claimed embodiments of *embryonic stem cells at the origin of somatic cells*, and *stem cells at the origin of blood, and various other tissues*, lack a written description. Thus, the cell types that are claimed are not adequately described by the specification. Although Applicants have amended the claims to recite "human

stem cells", this does not address the description for embryonic stem cells at the origin of somatic cells, or stem cells at the origin of blood and various other tissues. The specification fails to provide any description of embryonic stem cells at the origin of somatic cells, because embryonic stem cells are pluripotent cells isolated from an embryo, and are thus, not considered somatic cells. Furthermore, claimed embodiments, such as stem cells at the origin of blood and various other tissues, fails to have a description, because the skilled artisan could not envision such stem cells, as encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and newly added claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 1/25/05.

Applicants argue that the specification provides clear and simple guidelines for the skilled person to depart from the specifically illustrated human HSCs and TGFβ, to work with other human stem cells. Applications argue that the level of unpredictability in the art, which is underlined by the Examiner in the prior Office action, has been considerably reduced, by excluding the scope of the invention to stem cells from species other than human and primate. Furthermore, Applicants

argue that populations of human stem cells, that are different from hematopoietic progenitor cells, described in the specification, are actually simpler for the skilled artisan to deal with than those exemplified in the specification. Applicants argue that indeed, the population of hematopoietic progenitors cells is a rather heterogeneous population of cells, whereas populations of human ES cells, or keratinocyte stem cells are more homogenous and allow an implementation of the invention by the addition of TGFβ, instead of the more elaborate steps of successively culturing the cells with anti- TGFβ, and TGFβ, that are undertaken in the example in the working example. Applicants finally argue that the ordinarily skilled person is able to practice the claimed invention with the specific differentiation medium adapted to the particular population of cells to be obtained. See pp. 13-15 of the Response.

These arguments have been considered, but are not persuasive. The prior Office action addresses two key issues of enablement: that of the particular stem cell that is to be used, and the particular inhibitor that would be used in order to practice the claimed method. The breadth of the claims encompasses inhibitors that are products of genes which control cell development with respect to cell differentiation and/or cell division, inhibitors of cyclin-dependent kinases, factors which control apoptosis or aging and cytokines (such as interferons or TGF-beta). See p. 3, lines 10-15 of the specification. The breadth of the claims now recites "human stem cells". However, this encompasses a wide variety of cells, as contemplated by the specification as undifferentiated, pluripotent, or multipotent cells. The working example in the specification is a prophetic working example that fails to provide specific guidance to practice the claimed invention. There is no guidance in the specification that the HSCs are maintained in an undifferentiated cells, while allowing cell division of the HSCs. Applicants' arguments with regard to the simplicity of culturing cells other than HSCs is not persuasive. The J. of Cell Science article provided by Applicants (Fortunel *et al.*) is post-filing art. An

invention must be enabled at the time of filing. See MPEP §2164.01. Fortunel *et al.* teach culturing of primitive keratinocytes at very low concentrations in order to show an induction of expansion. The scope of the Fortunel article is not within the scope of the claimed invention. The claims are broadly drawn to any stem cell (which encompasses primitive keratinocytes, but also encompasses a wide variety of other stem cells). The claims are further broadly drawn to utilizing any amount of a particular inhibitor of cell development. Fortunel *et al.* is directed to utilizing a very low concentration of a particular inhbitor, TGFβ. Furthermore, the arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that other stem cells would be simpler to maintain than the exemplified human HSCs.

It is reiterated, as in the previous Office action, that the breadth of the claims encompass a wide variety of cell types and factors that would be used as inhibitors of cell development. The state of the art of culturing stem cells shows that it would require undue experimentation for one of skill in the art to determine the conditions for culture any human stem cell with any inhibitor of cell development, in order to maintain a non-differentiated state, but allowing cell division of the cells. See also, Thomson *et al.* and Xi *et al.*, cited in the prior Office action. Accordingly, in order to practice the claimed invention, the skilled artisan would have to first isolate a particular stem cell, determine a particular factor that results in the inhibition of differentiation, but allows for cell division and further, determine the amount of factor needed to provide sufficient inhibition of differentiation. The claims recite steps of administering "an effective amount" of an inhibitor to the stem cells. However, the specification provides no guidance or teachings with regard to how much an "effective amount" encompasses. As evidenced by the state of the art, as well as the predictability in the art, it would have required undue experimentation

for one of skill in the art, to determine how much is considered an "effective amount" with regard to the breadth of the claims.

Thus, when taken with the lack of any particular and specific guidance provided by the specification for the specific factors, specific stem cells and specific conditions to culture the stem cells in, to achieve inhibition of differentiation, yet allow for cell division; the lack of working examples, the breadth of the claims, with regard to any particular stem cells and any particular factor, it would have required undue and unpredictable experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The prior rejection of claim 15 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicants' amendment to the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The prior rejection of claims 1, 3-7, 8-10, 12, 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Williams *et al.* [**Nature**, 336:684-687 (15 December 1988)] is withdrawn in view of Applicants' amendment to the claims, now reciting human

stem cells. Williams teaches culturing mouse ES cells, and does not teach culturing human stem cells.

The prior rejection of claims 1-16 and newly added claim 19 under 35 U.S.C. 102(b) as being anticipated by Xi *et al.* is maintained for reasons of record advanced in the prior Office action.

Applicants argue that Xi does not teach multiplying stem cells using an inhibitor of cell development in combination with an anti-inhibitor. Furthermore, Applicants argue that the experiments taught by Xi does not teach how to multiply stem cells without differentiating them, using TGFβ. Applicants argue that Xi focus on later progenitors, rather than the stem cells described in the example of the present application, and that they particularly work with megakaryocyte progenitor. They further teach that PF4 does not seem to inhibit the proliferation of the high-proliferative potential mixed colony-forming units megakaryocytes. Applicants argue that this is what a low concentration of TGFβ is able to achieve in a reversible manner, and thus, Xi *et al.* do not anticipate the claimed invention. See pp. 16-17 of the Response.

This is not persuasive. The active method steps of the claims only require administration an inhibitor of cell development to maintain to human stem cells. Whether or not Xi *et al.* focus on later progenitors is irrelevant to the breadth of the claims. They teach a particular factor, TGFβ, and administration of this factor to human stem cells. Thus, because they teach each step of the method, they necessarily will arrive at the same effect as that which is instantly claimed.

Xi compare the mechanisms of platelet factor 4 (PF4) and TGF-β1 on the growth of megakaryocyte (MK) progenitor cells in $CD34^+$ cells. Xi teach that although both PF4 and TGF-β1 inhibit MK development from $CD34^+$ cells, they show different effects in this inhibition. Where the inhibition of PF4 is found to be reversible, the inhibition using TGF-β1 is not. See *Abstract* and p. 270, *Discussion.*

Xi teach using 10^5/ml of $CD34^+$ cells and incubating the cells with either 5 mg/ml of PF4 and 1 ng/ml of TGF-β1. See p. 266, 2nd column, Liquid culture system. The cells were then incubated for 2 days. See p. 267, 1st column, 1st sentence. The effects of this culturing were then analyzed by direct immunofluorescent assays and by flow cytometry. See p. 267, 1st column.

Accordingly, Xi anticipate the claimed invention.

The prior rejection of claims 1, 2, 4, 5-9, 12, 14, and newly added claim 19, under 35 U.S.C. 102(e) as being anticipated by Moore *et al.* is maintained for reasons of record.

Applicants argue that Moore *et al.* do not teach the claimed invention because they do not use culture conditions such as those used in the present invention to amplify the CD34+/CD38- subpopulation, and that instead, IL3 is used in the control stem cell assay, and yet it is known that IL-3 differentiates early progenitors. Applicants argue that Moore *et al.* studies the effects of pylartin on CD34+ cells, but they are not necessarily representative of the stem cell compartment, because the stem cell compartment represents only 1% of the CD34+ cells. See p. 18 of the Response.

This is not persuasive. Applicants are arguing limitations that are not in the claims. Although Moore *et al.* do not teach particular culture conditions taught in the particular examples, those conditions are not required or recited in the claims. Moore *et al.* anticipate the claimed invention because they teach each step that is required by the claim, and thus, would necessarily arrive at the claimed invention. CD34+ cells comprise stem cells, as recited in the claims. Nothing else is required. There is no limitation in the claims as to what sort of stem cell is required or recited, because the claims broadly recite "human stem cell". Accordingly, it is maintained that Moore *et al.* anticipate the claimed invention.

Moore teach methods of regulating hematopoietic processes by providing a factor and method of using the factor to maintain and expand hematopoietic progenitor cell populations. See col. 2, lines 47-52. They teach a protein, pylartin, which can be used in culturing hematopoietic stem cells of various species which allows the preservation of the progenitor cells yet, is able to inhibit the differentiation of the cells. See col. 6, lines 22-47. They teach that the pylartin protein can be used in conjunction with flk2 ligand in an amount sufficient to selectively expand the progenitor cells, without inducing differentiation. See coll. 8, lines 18-22. They teach the isolation of the pylartin protein from kidney beans and hyacinth beans. See Example 1. They teach the that the pylartin protein preserves both human and murine hematopoietic progenitor cells *in vitro* when cultured with the cells. See Example 2. They teach that when used in conjunction with IL1 and FL, human hematopoietic progenitors were preserved for 2 weeks, and that the number of colonies derived from the functional progenitors is several times greater than compared to controls. In particular, they teach that cord blood mononuclear cells were cultured at a concentration of 800,000 cells in 4 ml. See Example 8.

Accordingly, Moore anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the

subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12 and newly added claim 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzfeld *et al.* This rejection is maintained for reasons of record advanced in the prior Office action.

Applicants argue that this abstract does not disclose or suggest how human stem cells can be multiplied *in vitro* while being maintained in a non-differentiated state. In particular, Applicants argue, that the abstract does not disclose or suggest the beneficial effect of adding an inhibitor of cell development such as TGFβ for maintaining a "stem" state during cell divisions, further, the art does not teach or suggest how to use TGFβ, and anti- TGFβ in a sequence combination or cyclically. Indeed, Applicants argue that the skilled artisan would be deterred from the abstract by using TGFβ or anti- TGFβ to multiply non-differentiated stem cell, because they conclude the possibility of using transient activation of HPPQ as an excellent tool to mark stem cells and follow their development, which suggests further differentiation, instead of maintaining them in a non-differentiated state. See pp. 19-20 of the Response.

This is not persuasive. Applicants are arguing limitations that are neither recited nor required by the claims. There is no requirement that the abstract disclose a beneficial effect of adding TGFβ. The art teaches the steps required by the claims, and thus, provides sufficient teaching and motivation to arrive at the claimed invention. Hatzfeld teach that TGF-β down-modulates various cytokine receptors, and that this effect can be suppressed within 6 hours by the addition of

anti-TGF-b antibodies, or antisense nucleotides. Hatzfeld study the release from TGF-β growth inhibition of high proliferative potential-quiescent primitive progenitors to understand whether this inhibitor is a central regulator of the stem cell compartment. They teach that these observations are used in developing an *in vitro* assay which combines receptor induction by anti-TGF-β together with optimal cytokine stimulation which can be performed using non purified hematopoietic progenitors. They teach that this method can render quiescent primitive progenitors responsive to optimal combinations of cytokines to improve the *in vitro* expansion of clinical samples. Thus, they teach the neutralization of an inhibitor of cell development (i.e., TGF-β).

Although Hatzfeld do not specifically teach that the cell divisions range from 1 to 100 (as required by claims 4, 5), it would be obvious for one of ordinary skill in that by allowing the cells to divide, there would be at least one cell division that occurs. Furthermore, although they do not specifically teach a cell concentration of about 1 to about 10^{10} cells (see claim 8, for example), it would be obvious for one of ordinary skill in the art that in order to implement the claimed invention there would have to at least be one cell present. Accordingly, the claimed invention would be rendered obvious by the teachings of Hatzfeld.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER